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Chapter 6

Multidrug Resistance in Zoonotic Pathogens: Are Medicinal Plants a Therapeuthic Alternative?

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.81703

Abstract

Multidrug resistance (MDR) represents a complex phenomenon, caused not only by nondiscriminative antibiotic therapy in both human and animal medicine but also by the transfer of resistance genes between different bacteria. Animals besides different environments embody a niche for the development of resistant microbiomes, representing a serious threat to people not only as contacts but also as consumers/tourists. The epidemiological cycle of MDR bacteria is closed by changes in either their hosts or in their habitats. To prevent further spreading of MDR, natural solutions are investigated as efficacy, including in this category various compounds isolated from medicinal plants (quinones, flavones, flavonoids, and flavonols, tannins, coumarins, terpenoids and essential oils, alkaloids, lectins and polypeptides, etc.). The results of such studies are valuable for the medicine, but could the medicinal plants cover the gap for humans, animals, and the environment? This chapter aims at trying to answer this question.

Keywords: zoonotic bacteria, animals, multidrug resistance, medicinal plants, MIC/MBC

1. Introduction

Animal use paralleles, for millennia, with the development of human society; these sentient beings serve not only as working tools, weapons, and food source, but also as pets and companions. This closely interdependent and complex coexistence in a sometimes very narrow ecological niche led to an occasionally interchangeable, closely related pathology. Diseases that evolve at the level of human-animal-environment interface could negatively interfere not only with health at all levels, but also impact on economy and implicitly on welfare and social status

of the population [1]. Human and animal matrices reciprocally transfer emerging or reemerging pathogens by direct contact, through food/feed and water, or sharing the habitat, and this occurrence gives rise to the so-called zoonoses [2]. A significant number of zoonotic disease are caused by bacteria, for control, treatment, and prevention of which antibiotics represented, and still represent a powerful tool. Nonetheless, antibiotic treatments, which spread exponentially, especially in preventing diseases ignoring the real infectious pressure, created a very tough, artificial selection, the survival rate of resistant bacteria becoming higher and higher [1]. One of the crucial, but sometimes disregarded sectors in generating and spreading antimicrobial resistance and increasing the public health risks is represented by animal farms, encompassing intensive raising technologies [3]. A proper understanding of the main features of this sector in segments such as the increased spreading of resistant bacteria due to the presence of a broad susceptible population, supports the disease-control strategies, management of global health risks, and improvement of health security [1]. Institutions such as World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), World Organization for Animal Health (OIE) co-work with international bodies, political actors, researchers, universities, and other institutions to preclude and control these hazards and the multiple impacts exerted by encouraging multiple collaborations, developing short-, mid-, and long-term strategies and efficient tools encouraging their implementation and use and also involving the relevant decision makers and stakeholders [4].

Since the discovery of penicillin by Fleming in 1928 [5], "antimicrobial" use has spread through the fields of human and animal health, to environment including various habitats and thus wildlife (**Figure 1**). Not only bacteria from the various natural animal niches became resistant, but also the antibiotic resistance was indicated in bacterioplankton [6] and proved to

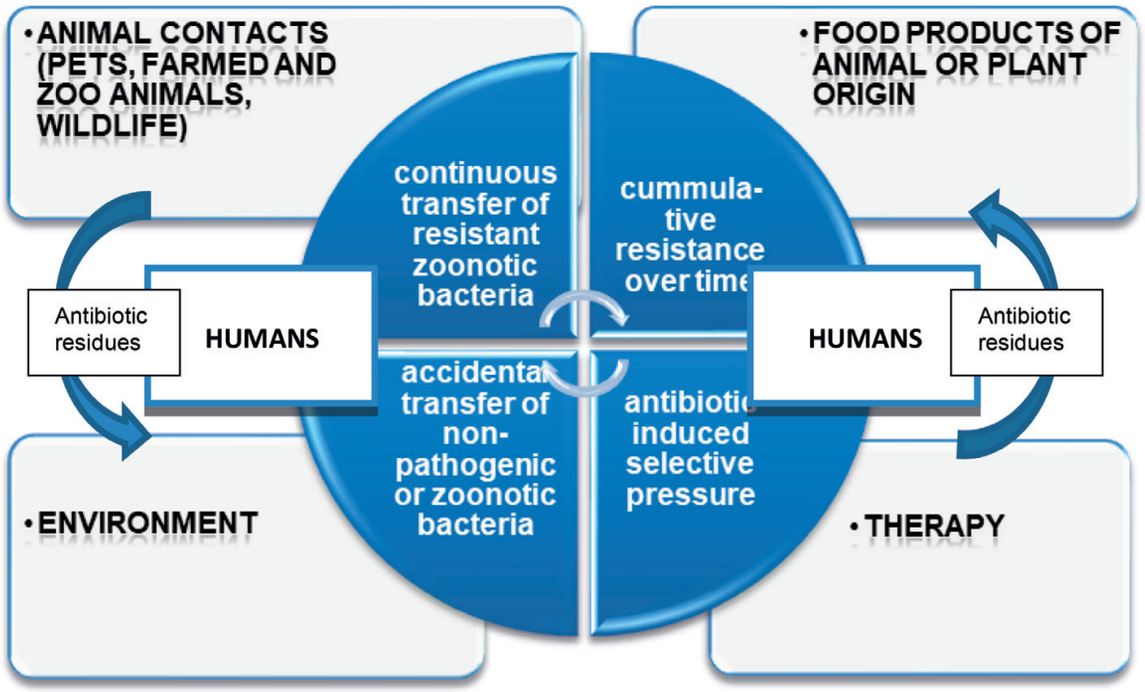

Figure 1. Main sources for human exposure to antibiotic-resistant bacteria (from [37]).

http://dx.doi.org/10.5772/intechopen.81703

be dependent on geochemical conditions in the soil [7, 8]. Antibiotic resistance seems to be positively strongly correlated with the heavy metal pollution of the environment [7, 9–12].

Without a scientifically supported knowledge, vegetal extracts from various sources were used for millennia to treat infections, diminishing the negative impact of numerous bacteria. Modern medicine requires scientific evidence to support and confirm the expected therapeutic efficacy [13]; thus, the number of researches on plant extract properties augmented over the years and currently belongs to a worldwide recognized strategy aimed at identifying biologically active compounds that represent a viable alternative to synthetic drug substances demonstrated with various inconveniences (multiple side effects, nonselective toxicity, high production costs) or that have lost their initial efficacy [13]. Although different trends were described over the years, natural source importance was not minimized, as they provide key scaffolds for drug development particularly in case of antimicrobial drug development [13–19].

Briefly, the use of medicinal plants and their extracts as antimicrobials for therapy, although known for centuries, is far from being a closed subject. Medicine and biochemistry show a continuously increasing interest to this field, resulting in the introduction in practice of novel preparations, gaining new meanings within modern prophylactic and therapeutic alternatives.

Since the discovery of new molecules is apparently slower compared to bacteria resistance level increase, an integrated approach allowed the screening of various plant genera, confirmation and characterization of their antimicrobial properties (in terms of antimicrobial spectrum, minimum inhibitory concentration, minimum bactericidal concentration), identification of active compounds, and of certain mechanisms of action, which led to the expansion of the application range: therapeutic products for human health and animal health, performance enhancers or feed additives for farm animals, products for plant crop protection, food preservatives [13, 18, 20–22], etc. In the last decades, pharmacognosy studies on medicinal plants cleared numerous aspects of their bioactivity, certain ways, and sites of action of phytomedicinal compounds [23, 24]. With the progress of science and analytical laboratory methods, it has been proven that extracts from plants, containing numerous chemically active compounds such as alkaloids, tannins, polyphenols and others, could actively inhibit bacterial growth and simultaneously improve the immune response in the host by changing or inhibiting protein-protein interactions. This type of combined activity does not allow, apparently, the development of resistance [25].

Literature gathers a multitude of scientific studies that support the use of whole plant extracts in therapeutics, and the vast majority of researchers indicate medicinal plants as a viable alternative for the antimicrobials [13, 24, 26–29].

A different therapeutic approach considers plants as source for individual active compounds, not as whole extracts or solvent-based active principle mixtures. It is estimated that over 12,000 secondary plant metabolites were isolated, representing less than 10% of the total compounds found in plants. The major active molecule groups were defined as: phenolics and polyphenols, terpenoids and essential oils, alkaloids, lectins and polypeptides, polyamines, isothiocyanates, thiosulfinates, and glucosides. Nevertheless, the extraction and purification costs act as limiting for the use of individual compounds [28].

These data provide solid bases for the development of safe and effective drugs that can be used in human and veterinary medical practice [13, 30, 31].

However, mostly due to limitations associated with natural products classical screening methods, large pharmaceutical companies' interest in this category remained relatively low for several years. This particular disadvantage was significantly overcome due to the most recent strategies for natural product screening that involve an integrated multidimensional evaluation of botanical, phytochemical, and biochemical aspects, as well as advanced methods such as metabolomics and proteomics that enable the rapid identification of new compounds and production of target molecules, respectively [32, 33].

This chapter represents an overview of the most important zoonotic bacteria in terms of complexity, diversity and antimicrobial resistance, and resumes scientific data on bioactivity of medicinal plants against multidrug-resistant zoonotic bacteria isolated from animal cases.

2. Zoonotic bacteria complexity and diversity

Zoonotic bacteria are among the most important causes of morbidity and mortality in human, and their importance is recognized and stated by several international and national organizations [34, 35]. Furthermore, given the abundance of scientific proof of their impact on human health, international control and prevention strategies are currently implemented worldwide. In addition, numerous retrospective and prospective studies are conducted by specialized interdisciplinary research groups in order to provide more and updated knowledge on the etiopathogenesis of both already established and emerging or reemerging diseases. The economic consequences cannot be minimized, since the international protocols involve disruptions of national, regional and global trade, and substantial losses associated with animal culling and disposal of the carcasses. To acknowledge the zoonotic importance and the economic impact, certain bacterial diseases are also listed by OIE and require official notification [34]. The most common and important bacterial diseases with confirmed zoonosis status are anthrax, brucellosis, bovine tuberculosis, campylobacteriosis, listeriosis, leptospirosis, salmonellosis, psittacosis [36–38], etc.

Starting with 2010, the WHO, FAO, and OIE identified and issued priority areas that included zoonotic diseases and underlined the need for multidisciplinary collaboration to address health threats at the human-animal-ecosystem interface under the one-health concept. The one-health concept or paradigm allows the comprehensive description of the complex epidemiology in zoonotic diseases. Among the most compelling examples of the One Health paradigm, food-animal-associated zoonoses are distinguished and are monitored worldwide. It is mostly, but not exclusively, the case of foodborne diseases, with top ranked pathogens such as *Salmonella*, *Escherichia coli*, *Campylobacter* [37, 39], etc.

Salmonella serovars and *Escherichia coli* pathotypes were isolated from many specimens of mammalian, avian, reptilian, and amphibian origin, fish, and insect, as well as from plants, soil, and water origin; hence, the main route of transmission involves consumption of contaminated

foods of both animal and vegetal origin: poultry, beef, pork, eggs, milk, fruit, vegetables [37, 39, 40], etc.

Other pathogens' transmission is related to occupational hazards, and one of the most resourceful bacterium in this regard is represented by livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA), in particular the clonal complex (CC) 398 [25, 41–43]. Its first description was based on the isolation from pigs, pig handlers, and their close contacts, followed by reports involving livestock and livestock-derived food products in several countries, particularly in regions with high-density pig farming from Europe, Canada, Asia, and the USA [25, 42, 44, 45]. Grounded on recent data, colonization of LA-MRSA among persons occupationally exposed to pigs, cattle, or poultry appears to be very frequent and risk of developing MRSA infections is relatively elevated [41, 42]. The first exposed persons are not only at the risk to develop infections, but also they presumably represent the source for LA-MRSA transmission to household members [43, 46] and other parts of the human population [41], explaining the isolation of LA-MRSA from hospitals and other healthcare facilities' environment.

A substantial scientific database was collected over decades providing relevant information on zoonotic diseases that originate from farmed or food animals [37, 38, 47], but more and more figures suggested pets and wild animals were significant sources and reservoirs of zoonotic bacteria [48–52]. Regarding pets, the great majority of the studies are focused on cats and dogs [53], but lately the range of animal species kept within households diversified to encompass rodents, rabbits, ferrets, birds, amphibians, reptiles, and ornamental fish [49]. Comparing the amount of literature data, pet-associated bacterial zoonoses are considered as a relatively neglected area compared with foodborne zoonoses [49]; thus, future studies are needed to understand the complexity of epidemiological links in these cases.

The main study approach is similar to farmed animals and targets the two main categories of sources: (1) sick animals and (2) asymptomatic carriers, considering that pets may be infected or colonized with a wide variety of bacteria pathogenic to animals and people. With respect to transmission routes, a close contact between pets and owners represents a peculiarity that suggests primarily the direct contact; petting and playing with pets along with licking or minor physical injuries (usually affecting the skin on the hands) may be associated with local or systemic pathologies especially in risk categories that include young, old, pregnant, and immunosuppression individuals. Secondly, the food, water, and the environment may be contaminated by pets' fecal and skin microbiota [54, 55].

The above-mentioned aspects are reunited due to the increasingly popular trend of feeding raw meat-based diets (RMBDs) [56–58], with several studies underlining the serious risks to both animal and human health, given the laboratory confirmed presence of zoonotic bacteria and parasite pathogens in commercial RMBDs. Fresh, refrigerated, and frozen RMBDs may represent the source of *Escherichia coli* serotype O157:H7, extended-spectrum beta-lactamases-producing *E. coli*, *Listeria monocytogenes*, *Salmonella* species such as *S. typhimurium*, *S.* Heidelberg, and *S.* Kentucky [54, 56, 57, 59, 60]. Feces appear to represent an important source of Gram-negative bacteria with zoonotic potential, and several studies indicated a positive correlation between the raw meat feeding and *Salmonella*-active fecal shedding. Although it may not

be representative for the general population of dogs, a special canine category was investigated in this regard—the case of dogs that participate in animal-assisted interventions (AAIs), also named "therapy dogs": since these animals commonly interact with immunocompromised people, the risks cannot be minimized [54, 56, 57, 61].

3. Multidrug resistance in animals

Antimicrobial Resistance Global Report on surveillance [62], issued in 2014 by WHO warned, based on surveillance data recorded, on the major problem represented by antibiotic resistance in a "postantibiotic era. "This definition underlined that most antibiotics, while considered a panacea, were broadly misused in both humans and food-producing animals, thus leading for widespread MDR. In parallel with the discovery of new antibacterial classes of compounds, the induction of resistance was followed closely by the drugs selecting the most resistant of the pathogens, which further spread [62].

One of the less regarded, yet significant sectors in spreading MDR, is represented by the animal segment, and little is known about the epidemiology of MDR in food animals and lesser in wildlife. Similarly to human medicine, veterinary antibiotics in use fail to control not only infections related to conventional agents but are also ubiquitous and commensal bacteria turned into aggressive pathogens. Not only antimicrobial use to control medical situations, such as herd- or flock-based infections (pneumonia, neonatal infections and infections occurring in immune-suppressed animals, surgeries, etc.) [62], but also the use of antimicrobials as growth enhancers in food-producing farmed species (poultry, swine, and cattle) increased the risk represented by animals in spreading MDR. Morbidity and mortality caused by bacteria resistant to commonly used and available for veterinary antibiotics are not the single causes for economic losses in farmed animals. Supplementary cost must be added for food control for antibiotic residues and resistant bacteria in food and disposal of contaminated items. There are many researches on the use of quantitatively active antimicrobial ingredients in farmed animals, showing the amount far exceeds that used in humans.

Enterobacteriaceae represent a large bacteria family, including numerous genera inhabiting human and animal gut of which some synthesize endotoxins. The best known representatives, *E. coli* and a broad variety of *Salmonella spp*., were subject to abundant studies. Not only these, but also some other representatives of the family show MDR and also resistance to antibiotics such as last-generation beta-lactams (i.e., carbapenem) used to treat severe bacterial infections and considered to be "the last line of antibiotic defense." A smaller group of carbapenem-resistant Enterobacteriaceae (CRE) proved to be carbapenem-nonsusceptible and extended-spectrum cephalosporin resistant, and include *Escherichia coli, Enterobacter aerogenes, Enterobacter cloacae* complex, *Klebsiella pneumoniae*, or *Klebsiella oxytoca* [63]. These species are also found in animals: the *Enterobacter* complex as commensal microflora in the intestinal tracts of mammals and fish and also pathogenic for insects [64], *E. coli* in swine, dairy cows' mastitis [65, 66], *Klebsiella oxytoca* not only in bovine mastitis [67], but also in pets [68].

Multiple antibiotic-resistant bacteria emerging in dairy cows' mastitis as a result of extensive/uncontrolled drug use, biased therapy, horizontal gene transfer, and/or spontaneous genetic mutations pose an increased health risk to humans by contaminating milk and milk products. Virulence genes in connection with antimicrobial define pathogenic, but also certain commensal strains of *E. coli*, emphasizing the risks of fecal contamination of animal-derived, including milk products, as an important source for human outbreaks. Furthermore, the severeness of illness is increased in *E. coli* by the association of MDR with Shiga-like toxin (*stx1* and *stx2*) genes' presence. For example, resistance toward several active substances from commercial products recommended for bovine pathologies: penicillin-streptomycin, tetracycline, neomycin, ampicillin, and amoxicillin/clavulanic acid was found to different extents (MAR 0.2–0.80)—was found in 125 isolates sampled from healthy dairy cows. Multidrug-resistant phenotypes (resistance to more than four antimicrobials) were recorded for 12 isolates (9.6%). The molecular analysis pointed out the presence of *stx1* gene in case of 20 strains and *stx2* for 11 strains, respectively. The presence of Shiga-like toxin genes (*stx1* and *stx2*) and high MAR index highlight the risk associated with human exposure in terms of possible contamination of milk and dairy products provided by the bovine farms. These results support compulsory food hygiene and safety measures throughout the production chain, to minimize or eliminate the contamination risk for the products provided by these farms [Crisan et al., unpublished data, 2018].

A study conducted in Canada by Finley et al. [56] indicated for commercially available canine raw food diets, an overall *Salmonella* prevalence of 21%, with chicken as an ingredient for 67% of the *Salmonella*-positive diets. Eighteen distinct serotypes displaying resistance toward 12 of the 16 antimicrobials tested, and a predominant pattern of ampicillin and tetracycline resistance entitled the authors to conclude on the need for implementing regulatory guidelines for the production of these diets aimed to reduce or to eliminate the associated risks for pets and the contact people.

Also, outbreaks of human salmonellosis related to exposure to animal-derived pet treats (pig ear, beef steak patty dog, and pet treats of seafood origin) have been reported in Canada, with the laboratory confirmation of *Salmonella* contamination in case of mentioned pet treats and identification of the following serotypes: *S.* Bovismorbificans, *S.* Give, *S.* Derby, and *S.* Typhimurium var. Copenhagen. The overall prevalence of 4% was regarded as lower compared to data reported in 1999, but the isolates showed resistance to up to seven antimicrobials [56]. A significant higher prevalence with 41% (65/158) of samples found positive for *Salmonella* was reported in case of dog treats derived from pig ears and other animal parts randomly collected in USA [28].

Updates on the antimicrobial resistance trends are needed in order to select the most suitable choices for the antibacterial therapy particularly in case of methicillin-resistant *Staphylococcus aureus* (MRSA) infections. Regarded as an opportunist organism, MRSA is responsible not only for localized skin and soft-tissue infections, but also for invasive forms such as septicemia and toxic shock syndrome [45]. Severe clinical outcomes and added costs justify further research for alternative treatments.

Due to the high diversity of MDR bacteria isolated from numerous animal sources and food of animal origin, an integrated meta-analysis of data could support the upgraded short-, medium-, and long-term strategies to control antimicrobial resistance and its further development, which in their turn are important for preventing the emergence and cross-country/continent spreading of resistant strains [69].

4. Medicinal plants as antibacterial agents

Numerous researchers studied the healing effects of plants and their extracts along with their beneficial effects in healthy organisms. Nowadays, plant-based therapy benefits of solid scientific support the individual chemical components or their combinations showing antimicrobial and anti-inflammatory activity, immune-stimulating potential, or anticancer effects. Since prevention is the key to good health, the researchers investigated the possibilities of using vegetal preparations to preserve health: (a) indirectly, by stimulating both innate and the adaptive immune response to antigens of various kinds and also (b) directly, by exerting either a bacteriostatic or preferably a bactericidal effect [70].

Apparently simple, the selection of plants or their extracts to be used for specific therapeutic purposes embodies the involvement of numerous factors, from health to economic impacts (**Figure 2**).

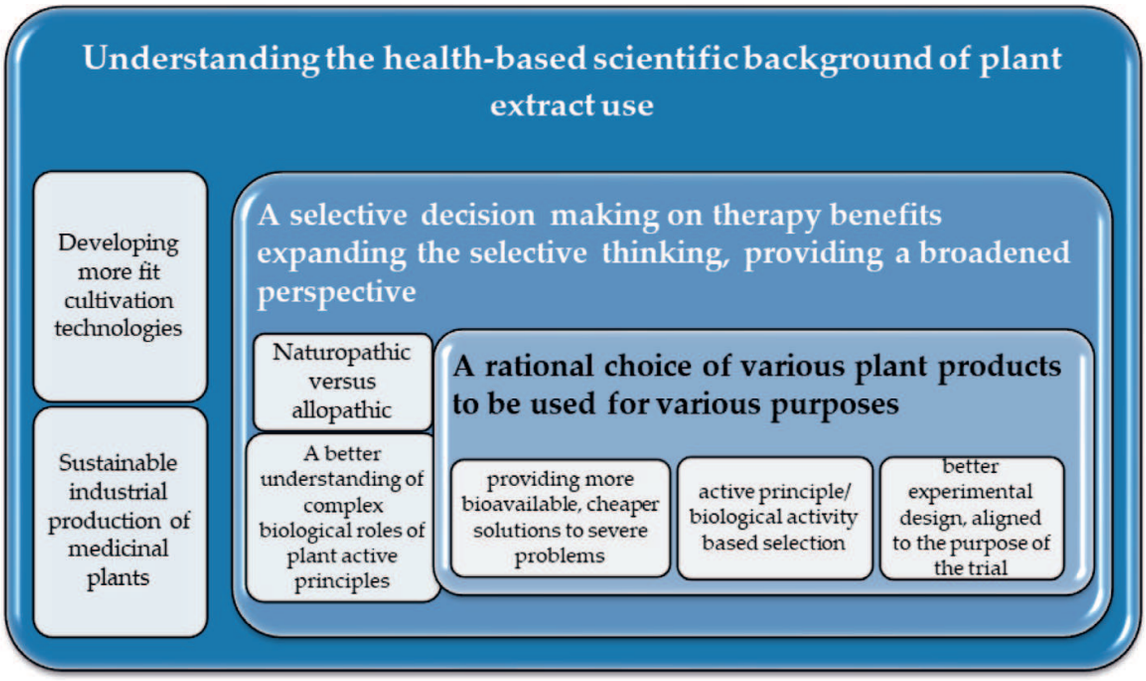

Figure 2. Different steps of the decision-making process in plant extract use for therapy.

http://dx.doi.org/10.5772/intechopen.81703

4.1. Plant extracts acting against bacteria indirectly: immunological uses

Current trends in medicine tend to include natural products in therapy, without mixing allopathic and homeopathic treatments, the latest gaining more and more in comparison with chemically obtained compounds. The WHO list of 252 basic and essential drugs includes 11% of medications exclusively of flowering plant origin [71].

Vegetal extracts from various plant origins are used more and more, with a favorable activity in diminishing the negative impact of numerous microbial agents or in improving the innate or acquired resistance of the body to infections [17, 18, 72].

Classical therapeutic protocols supplemented with vegetal extracts could increase the protective capacity of the individuals, by their complex action mechanisms, which stimulate immunity. This pattern is actually applied in veterinary medicine, where certain stress-induced changes, caused by intensive raising/farming of food species, could be corrected in this manner [73–76]. Moreover, active principles proved to be potent in restoring the immune reactivity in individuals with induced or innate immunosuppression [77–82].

Vaccines against bacterial diseases represent one of the most powerful tools for prevention and control. Within this framework, researches on the immune stimulating activities of vegetal extractions were successful, with obvious immune modulating effects. Due to improved bioavailability as compared to conventional drugs, combined with immune modulating potential, the question on plant extracts as potential adjuvants emerged for vaccines broadly used to prevent infectious diseases, in both humans and animals. An appropriate understanding of adjuvant potential of vegetal extracts and experimental design to investigate these possibilities would lean on a good knowledge of general action mechanisms of vaccine adjuvants.

4.2. Direct antibacterial activity of plant extracts

Antimicrobial effects of plant extracts on clinical isolates from farmed and pet animals and their potential use to improve health and lower the risk for humans were illustrated by experiments aiming to investigate the influence of the plant taxonomy/chemical composition on the *in vitro* bacteriostatic/bactericidal effects.

Plant extracts were initially proposed as supplementary means in combined antibiotic and natural therapies; therefore, the synergism between plant extracts and antibiotics was also observed in experimental studies. In a complex research carried out to establish the antimicrobial effect of certain plants: *Achillea millefolium* (yarrow), *Caryophyllus aromaticus* (clove), *Melissa officinalis* (lemon-balm), *Ocimum basilicum* (basil), *Psidium guajava* (guava), *Punica granatum* (pomegranate), *Rosmarinus officinalis* (rosemary), *Salvia officinalis* (sage), *Syzygium jambolanum* (jambolan), and *Thymus vulgaris* (thyme) on bacteria resistant from 1 to 18 antibiotics: amikacin, ampicillin, cephalothin, cefpirome, carbenicillin, cefoxitin, chloramphenicol, ceftriaxone, cefotaxime, erythromycin, gentamicin, kanamycin, lincomycin, methicillin, nalidixic acid, netilmicin, norfloxacin, nitrofurantoin, penicillin, piperacillin, rifampicin, sulfonamide, sulfamethoxazole, tobramycin, tetracycline, vancomycin (*Proteus spp*., *Klebsiella pneumoniae*, *Shigella spp*., *Pseudomonas aeruginosa*,

Enterobacter aerogenes, *Escherichia coli*, *Staphylococcus aureus*) and susceptible collection strains (*Staphylococcus aureus* ATCC 6538, *Salmonella choleraesuis* ATCC 10708; *Pseudomonas aeruginosa* ATCC 15442), the authors indicated that clove (*Caryophyllus aromaticus*) and jambolan (*Syzygium jambolanum*) were the strongest inhibitors (64.2 and 57.1%) of the used bacterial strains. Furthermore, their activity was the most remarkable (83.3%) against the germs resistant to antibiotics, where their synergistic activity with the antibiotics was also observed. Interestingly, plants such as sage and yarrow, well known for their antiseptic properties, showed no effect on the tested MDR bacteria. Some of the plants showed in specific cases a homeopathic-like effect, i.e., clove, jambolan, pomegranate, and thyme extracts, when used in lower concentrations but combined with ineffective antibiotics against *Pseudomonas aeruginosa* [26, 27, 29, 83, 84].

Name	**Extract type**	***In vitro* efficacy against**	**Strain origin**	**Evaluation method(s)**	**Mechanism(s) of action**	**References**
Syzygium aromaticum and *Cinnamomum* > *Mentha spicata* L. and *Coriandrum sativum* L. > *Allium sativum* L. and *Nigella sativa* L.	Ethanolic extracts	MDR *E. coli*	Retail chicken meat samples	Broth microdilution	Not determined	[87]
Olea europaea	Ethanolic extracts	*E. coli* O157:H7 S. *enteritidis*	Reference laboratory	Broth microdilution	Inhibition of the biofilm formation for *S. enteritidis*	[16]
Origanum vulgare > *Thymus zygis Thymus mastichina*	Essential oils	*E. coli*, *Salmonella essen*, *Salmonella enteritidis*, ETEC, *Salmonella choleraesuis*, *Salmonella typhimurium*	Poultry swine	Broth microdilution	Not determined	[88]
Melissa officinalis > *Thymus vulgaris* and *Salvia officinalis*	Essential oils	*Staphylococcus aureus*, *E. coli Salmonella Enteritidis*	Bovine	Disc diffusion broth microdilution	Not determined	[89, 90]
Allium sativum L., *Elwendia persica (Bunium persicum)*, *Oryza sativa* L. and *Triticum aestivum* L.	Ethanolic extracts	*Staphylococcus aureus*, *E. coli*	Bovine	Disc diffusion broth microdilution	Not determined	[91]
Achyranthes aspera L., *Ficus carica*, *Malva parviflora*, *Vernonia species*, *Solanum hastifolium*, *Calpurnia aurea* Benth, *Nicotiana tabacum* L., *Ziziphus spina-christi*, *Croton macrostachyus*	Hydroalcoholic extracts	*S. aureus*	Bovine	Disc diffusion broth microdilution	Not determined	[92]

Table 1. Herbal extracts demonstrated to inhibit MDR zoonotic strains of animal origin.

Other well-known plants, which share immunological activity, from *Compositae* family, were further investigated for their antibacterial effects, following the principle of "the more the merrier." Echinacea, a popular plant in human medicine for its immune-stimulating and antiviral effects, also acts as an inhibitor for both tissue and bacterial hyaluronidase. This activity was considered to hinder the development and spreading of infection from localized to generalized [23, 24].

Another plant family, the Lamiaceae, has numerous examples of species with antibacterial activity. The investigation of their antibacterial activity against MDR, extended spectrum beta-lactamase-positive (ESBL), Gram-negative clinical isolates (*A. baumannii, K. pneumoniae, E. coli, P. aeruginosa*) of ethanolic extracts of *Mentha sp., Ocimum basilicum, Plectranthus barbatus*, and *Rosmarinus officinalis,* indicated that the minimal inhibiting concentration ranged from 0.5 to 2 mg/mL, while all extracts were effective against at least two of the tested bacteria [85].

Another plant from *Lamiaceae* with a less investigated antibacterial influence was considered as a potential therapeutic resource in bovine mastitis. Mastitis, one of the most economically impacting diseases of dairy cows due to subclinical status and difficult diagnosis, is heavily treated with antibiotics, leading to MDR in the involved bacterial strains. The lesser antibiotic efficacy, therefore, demands for therapeutic alternatives. In a study on the antimicrobial effectiveness of *Melissa officinalis* on the subclinical mastitis, microbiome carried out on several Romanian dairy farms ([93]), a variety of bacteria (*S. sciuri, Shigella spp. S. lentus, Acinetobacter baumannii, Chryseomonas luteola, Enterobacter cloacae, Escherichia vulneris*, etc.) were isolated with an MAR index up to 0.8 against amoxicillin+clavulanate, amoxicillin, chloramphenicol, cefoperazone, ciprofloxacin, and oxytetracycline. The *Melissa* tincture was less effective than the same plant essential oil (11.3 ± 3.6 versus 12.3 ± 4.3 mm), but comparable to amoxicillin, amoxicillin/clavulanic acid, and was higher than cefoperazone (total resistance). The efficacy depended more on the strain than on the solvent type also suggesting a therapeutic alternative to antibiotic treatment, as mentioned in the literature [86].

Most of the studies were carried out using reference strains, especially in case of the initial screening, but more recently, such assays also include clinical strains, both antimicrobial susceptible and resistant. **Table 1** summarizes relevant data on the ability of herbal extracts to inhibit MDR zoonotic strains of animal origin.

5. Conclusions

In spite of extensive research carried out on healing effects of plants, antibacterial effects included, the subject is far from being closed, the high variety of plant species providing a strong support for investigation. Although numerous researchers deal with the effects of individual compound against bacteria, those extracts containing multiple active substances and exerting simultaneously antibacterial and immune-enhancing effects are favored. Veterinary and zoonotic pathology, due to the presence of MDR bacteria, could equally benefit of the discovery of plant extracts with high antibacterial potential, useable separately or in combination with otherwise inefficient classical antibacterial therapies.

Acknowledgements

We acknowledge the financial support provided by the Romanian National Research Council of the Ministry of Education by the project PNII 61/2012 and the Hungarian Academy of Sciences for performing the research on antibiotic resistances in various environments and also plant extract effects on microbes.

Conflict of interest

None of the authors have any existing or possible conflict of interests, including financial, personal, or any other relationships, which could influence their scientific work.

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